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Preparation of Tritium-Labelled Phenethanolamines by Catalytic Reduction *

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SUMMARY

Tritium-labelled plenethanolamines have been readily prepared by catalytic reduction of corresponding α-aminophenones. Erythro *phenethanolamine racemates are exclusively formed by Pd-catalyzed reduction of α-alkyl-α-aminophenones. In one case, an α-aminophenone was further reduced by tritium to the phenethylamine, which has never been observed with catalytic hydrogenation under similar conditions. In this manner, three adrenergic agents have been labelled for metabolism and tissue distribution studies : sotalol-7-^3H hydrochloride, soterenol-7-^3H hydrochloride, and mesuprine-7-^3H hydrochloride.*

INTRODUCTION.

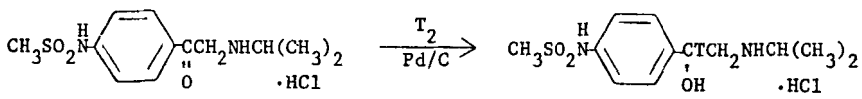
Although reduction of carbonyl compounds by the catalytic addition of tritium gas is a general method, the preferred procedure for preparing phenethanolamines such as epinephrine and norepinephrine has been reduction of the corresponding ketones with $NaBH_3T$ or $LiAlH_3T$ [1, 2]. The use of tritiated mixed metal hydrides for such carbonyl reductions has advantages of specific labelling of the carbonyl carbon atom and reaction conditions of room temperature and atmospheric pressure.

Unfortunately, reduction by metal hydrides of α-aminophenones containing an α-alkyl group results in a mixture of *erythro* and *threo*-phenethanolamine racemates, whereas reduction of such compounds by catalytic hydrogenation affords exclusively the more biologically interesting *erythro* racemates [3, 4]. For these reasons of stereospecificity, we have developed the reduction of α-aminophenones by catalytic incorporation of tritium gas.

* Part III of a series; for previous papers see ref. 3 and 5.

DISCUSSION.

The previously reported syntheses of 4′-(1-hydroxy-2-isopropylaminoethyl) methanesulfonanilide hydrochloride *(1)* *, 2′-hydroxy-5′-(1-hydroxy-2-isopropylaminoethyl)methanesulfonanilide hydrochloride *(2)* **, and of 2′-hydroxy-5′-[1-hydroxy-2-(4-methoxyphenethylamino)-propyl]methanesulfonanilide hydrochloride *(3)* *** were modified for small-scale preparation. Tritium-labelled samples of these agents were prepared to facilitate the study of their metabolism and tissue distribution.



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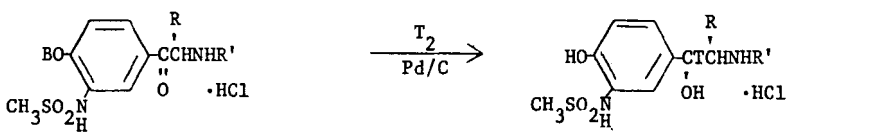


B = H or benzyl

2: R = H, R′ = $CH(CH_3)_2$

3: R = CH_3, R′ = CH_2CH_2-(4-OCH_3-phenyl)

Preparation of the nonlabelled aminophenone precursors has been previously reported [3, 5]. These aminophenones all react successfully with tritium gas and 10 % Pd/C to afford the 7-^{3}H-labelled phenethanolamines. Preferred reduction conditions include 50 % aq acetic acid solvent with 25 curies of tritium gas, about 2 :1 weight ratio of compound to catalyst, and stirring at room temp for 2-4 hours****. It has been shown that hydrogenolysis of a benzyloxy group occurs prior to carbonyl reduction [3], but would, of course, consume an extra mole of tritium.

The *erythro* and *threo* racemates of type *3* have been differentiated by the pmr coupling constants for their methine protons at C-7 and C-8 or the

* MJ 1999 or generic name sotalol hydrochloride, a β-adrenergic blocking agent [5].

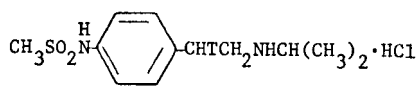
** MJ 1992 or generic name soterenol hydrochloride, a β-adrenergic agonist [3] and bronchodilator [6].

*** MJ 1987 or generic name mesuprine hydrochloride, a β-adrenergic agonist [3] and uterine relaxant [7].

**** The tritium reductions were done by New England Nuclear Corporation.

asymmetric centers. The presence of tritium at C-7 in the pure tritiated molecule abolishes this differentiating feature. However, the *erythro* and *threo* racemates have different solubilities and melting points, so the recrystallization of tritiated product, diluted with a sample of known *erythro* configuration, to constant mp and a single peak by radiochromatographic assay is taken as sufficient criteria for purity and identity. By catalytic reduction with tritium gas only *erythro 3* could be isolated, and no evidence for the *threo* racemate was seen. Even though there is no stereochemical requirement for *1* and *2* racemates, and they may be prepared just as well by a mixed metal tritide with the same aminophenones, their preparation by catalytic reduction is included to illustrate the generality of the procedure.

In the preparation of sotalol-7-^{3}H hydrochloride, *1*, a major impurity was detected by radiochromatographic analysis of the crude reaction product *. This additional product was identified as deoxysotalol-7-^{3}H hydrochloride, *4*, by comparison with a known unlabelled sample. Analysis of the crude reaction material indicated about 74 % was sotalol and 26 % was the deoxy product. By enriching the crude sample with pure unlabelled sotalol, and recrystallizing the free base from acetonitrile until a pure material was obtained, then converting to the hydrochloride salt, 49 % of the total activity was recovered as pure sotalol-7-^{3}H hydrochloride. By enriching the crude sample with pure unlabelled deoxysotalol and repeatedly recrystallizing the hydrochloride salts from methanol, 2 % of the total activity was recovered as pure deoxysotalol-7-^{3}H hydrochloride.



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In the preparation of *2*, 80 % of the radioactivity in the crude reaction product was soterenol-7-^{3}H hydrochloride by radiochromatographic analysis. No evidence was seen for deoxysoterenol in the crude reaction product, since soterenol hydrochloride has an R_f 0.23 in $CHCl_3$-EtOH (60 : 40) whereas deoxysoterenol hydrochloride has R_f 0.28 and the impurity peaks were R_f 0.39 and R_f 0.49. The aminophenone precursor may be the impurity at R_f 0.39, and it stained with the diazonium reagent Red "B" salt.

Radiochromatographic analysis of the crude reaction product for mesuprine-7-^{3}H hydrochloride, *3*, showed only trace impurities containing tritium

* Radiochromatographic analyses and radioactivity determinations were done by Dr. J. A. LaBudde and his group in this laboratory.

which may be toluene since the peak was at the solvent front. This was the most efficient and selective tritium reduction, even though an extra mole was consumed in hydrogenolysis of the benzyloxy group. No attempt was made to determine whether any of the non-labile tritium on the purified products was located on an atom other than the benzylic carbon, due to hydrogen-tritium exchange.

EXPERIMENTAL.

4'-(1-Hydroxy-2-isopropylaminoethyl-1-^{3}H)methanesulfonanilide hydrochloride (1).

A 50 mg sample of the corresponding aminophenone [5] was dissolved in 0.5 ml water and 1.5 ml glacial acetic acid containing 35 mg of 10 % Pd/C and 25 curies of tritium gas. The mixture was stirred at room temperature for 4 hours, filtered, and the filtrate diluted with 10 ml of 0.5 *N* HCl to remove labile tritium. After removing solvent under reduced pressure, the residue (835 mCi) was dissolved in 10 ml of 0.5 *N* HCl with 430 mg of sotalol hydrochloride, neutralized with 1.0 *N* NaOH and isolated as the free base. This material was repeatedly recrystallized from acetonitrile until chromatographically pure, diluted with another 71 mg of sotalol hydrochloride and completely converted to the HCl salt which was recrystallized from EtOH-isopropyl ether. This procedure yielded 289 mg of sotalol-7-^{3}H hydrochloride with 1.19 mCi/mg, mp 198.4-198.6° *, no depression on mixed mp with authentic sotalol hydrochloride. Radiochromatograms from three systems confirm purity and show R_f values identical to those for sotalol hydrochloride :

Whatman DE20 paper, pH 5.5, 0.02 *N* Na_3PO_4 — R_f 0.70.

Whatman CM50 paper, pH 5.5, 0.02 *N* Na_3PO_4 — R_f 0.23.

Eastman 6061 Chromogram, n-butanol/acetic acid/water (12 : 3 : 5) — R_f 0.48.

4'-(2-isopropylaminoethyl-1-^{3}H)methanesulfonanilide hydrochloride (4).

The acetonitrile filtrates from the above procedure were collected and evaporated. The residue was dissolved in MeOH-HCl with 550 mg of authentic deoxysotalol hydrochloride and repeatedly recrystallized from MeOH until chromatographically pure, yielding 203 mg of deoxysotalol-7-^{3}H hydrochloride with 71.5 μCi/mg and mp 265.5-267°, no depression on mixed mp

* All melting points were determined with a Thomas-Hoover capillary apparatus and are corrected.

with authentic deoxysotalol hydrochloride *. Deoxysotalol-7-^{3}H separates sufficiently from sotalol-7-^{3}H on one chromatographic system :

Whatman DE20 paper, pH 5.5, 0.02 *N* Na_3PO_4 — R_f 0.91.

2'-Hydroxy-5'-(1-hydroxy-2-isopropylaminoethyl-1-^{3}H)methanesulfonanilide hydrochloride (2).

A 50 mg sample of 2'-hydroxy-5'-(N-isopropylglycyl)methanesulfonanilide hydrochloride (prepared from the corresponding phenacyl bromide and isopropylamine [3], mp 238.5-239.5°) was dissolved in 1.0 ml water and 1.0 ml glacial acetic acid containing 25 mg of 10 % Pd/C and 25 curies of tritium gas. The mixture was stirred at room temperature for 4 hours, filtered, and the filtrate diluted with 10 ml dil HCl. After removing solvent by vacuum distillation, the residue (1.28 Ci) was combined with 1.15 g of soterenol hydrochloride and thrice recrystallized from MeOH-isopropyl ether until chromatographically pure. This procedure yielded 845 mg of soterenol-7-^{3}H hydrochloride with 1.27 mCi/mg, mp 203-204°, no depression on mixed mp with authentic soterenol hydrochloride. Radiochromatograms from three systems confirm purity and show R_f values identical to those for soterenol hydrochloride, by scanning 2 × 20 cm Eastman Chromogram strips coated with 100 mμ of silica gel :

EtOH/$CHCl_3$ (40 : 60)/1 % NH_4OH — R_f 0.46.

$CHCl_3$/MeOH/AcOH (75 : 20 : 5) — R_f 0.62.

MeOAc/i-PrOH/25 % NH_4OH (45 : 35 : 20) — R_f 0.80.

2'-Hydroxy-5'-[1-hydroxy-2-(4-methoxyphenethylamino)propyl-1-^{3}H]methanesulfonanilide hydrochloride (3).

A 60 mg sample of 2'-benzyloxy-5'-[N-(4-methoxyphenethyl)alanyl]methanesulfonanilide hydrochloride [3] was dissolved in 2.0 ml water and 2.0 ml glacial acetic acid containing 25 mg of 10 % Pd/C and 25 curies of tritium gas. The mixture was stirred at room temperature for 4 hours, filtered, and the filtrate diluted with 10 ml 0.5 *N* HCl. After removing solvent by vacuum distillation, the residue (427 mCi) was combined with 653 mg of mesuprine hydrochloride and recrystallized from EtOH-isopropyl ether until chromatographically pure. This procedure yielded 450 mg of mesuprine-7-^{3}H hydro-

* Prepared from 4-aminophenylacetonitrile with CH_3SO_2Cpyridine to 4-methanesulfonamidophenylacetonitrile, followed by Raney nickel hydrogenation to the phenethylamine and reductive alkylation with acetone and hydrogen/PtO_2. Elemental analysis, ir and nmr spectra for the product are consistent with deoxysotalol hydrochloride, which has mp 266.5-267.5°.

chloride with 685 μCi/mg, mp 187-189°, no depression on mixed mp with authentic mesuprine hydrochloride *.

Radiochromatograms on two systems using Eastman Chromograms confirm purity and show R_f values identical to those for mesuprine hydrochloride :

$CHCl_3$/MeOH/AcOH (75 : 20 : 5) — R_f 0.64.

MeOAc/i-PrOH/25 % NH_4OH (45 : 35 : 20) — R_f 0.83.

* Mesuprine hydrochloride exists in two polymorphic forms, one melting 187-189° and the other melting 201-203°. The low-melting polymorph was used exclusively in this work.

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